removed. The filtrate was treated with charcoal and evaporated to dryness *in vacuo*. The residue was dissolved in the minimum necessary amount of boiling water and the solution made just alkaline with ammonia. The precipitate formed by addition of excess of saturated basic lead acetate was collected, suspended in water (100 ml.) and treated with hydrogen sulphide to remove lead. After addition of excess $Na_2S_2O_4$, the lead-free filtrate was continuously extracted with ether. The ethereal extract was concentrated *in vacuo* to give a syrup which, on treatment with small volumes of water and chilling, gave a crude product, m.p. 105°, consisting mainly of 2:5-dihydroxytoluene. Recrystallization from water gave colourless needles, m.p. 124°, mixed m.p. with authentic 2:5-dihydroxytoluene (m.p. 125°), 125°. Yield 50 mg. (1 % of dose). (Found: C, 67·5; H, 6·6. Calc. for $C_7H_8O_2$: C, 67·7; H, 6·5 %.) The identity of the isolated metabolite with 2:5-dihydroxytoluene was further confirmed by paper chromatography and by the preparation of the dibenzoyl derivative, m.p. 118–119°, alone or mixed with an authentic specimen. 2:5-Dihydroxytoluene was similarly isolated from *o*-cresol urine. Yield 10 mg. from a total dose of 5 g.

DISCUSSION

The cresols are excreted principally as conjugates through the hydroxyl group, 60–72 % as ether glucuronide and 10–15 % as ethereal sulphate. Negligible amounts are excreted unconjugated and, as would be expected in compounds possessing a readily conjugable group, little conversion of the potential centre for conjugation or hydroxylation occurs. With regard to the extent to which such processes occur there exists a reciprocal relationship: in *o*- and *m*-cresols, where no conversion of the potential centre could be detected, hydroxylation occurs and in *p*-cresol, of which *p*-hydroxybenzoic acid was shown to be a metabolite, no significant hydroxylation could be detected.

SUMMARY

1. The cresols are excreted by the rabbit mainly as oxygen-conjugates; 60–72 % as ether glucuronides and 10–15 % as ethereal sulphates.

2. It has been shown by paper chromatography that *o*- and *m*-cresols are hydroxylated to a small extent and that *p*-cresol gives rise to some *p*-hydroxybenzoic acid.

3. *p*-Cresylglucuronide was isolated as a crystalline monohydrate from *p*-cresol urine and 2:5-dihydroxytoluene from *o*- and *m*-cresol urines.

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Further Observations on Changes in β-Glucuronidase Activity in the Mouse

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Increased β-glucuronidase activity in mouse liver or kidney was shown to reflect an increase in the proliferative activity of the tissue (Levvy, Kerr & Campbell, 1948). A similar relationship in uterus has been found to explain changes in the glucuronidase activity of this organ produced by certain sex hormones (Fishman & Fishman, 1944; Fishman, 1947; Kerr, Campbell & Levvy, 1949). Investigation of unexpected changes in glucuronidase activity in mouse tissues led to the discovery of new factors controlling growth in liver and uterus (Kerr *et al.* 1949). Further studies of these factors are described in the present communication. Additional examples of parallelism between the β-glucuronidase activity

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of a tissue and its state of proliferation, with particular reference to the actions of growth inhibitors, are also presented.

EXPERIMENTAL AND RESULTS

Methods

The assay of β-glucuronidase activity in tissue preparations and the measurement of uterine weight were carried out as described by Kerr *et al.* (1949).

The effects of certain steroid hormones on liver and uterine glucuronidase

In a previous communication (Kerr *et al.* 1949) it was shown that oestrone causes a marked rise in glucuronidase activity and in cell division in the livers of ovariectomized mice. This action was also seen in normal and castrated males, but not in intact females. In similar experiments with oestriol and oestradiol (Table 1), no change in liver glucuronidase activity was observed in male or ovariectomized female mice. Both compounds appeared to stimulate cell division in liver, but this effect was seen only with the larger doses studied, and at its greatest was slight compared with that produced by oestrone. Oestriol and oestradiol had the expected stimulant actions on uterine weight and glucuronidase activity (Fishman & Fishman, 1944; Fishman, 1947). It is not impossible that under different experimental conditions these steroids might show an effect on liver enzyme activity.

It has already been noted (Kerr *et al.* 1949) that testosterone antagonizes the effects of oestrone on liver and uterine glucuronidase. As can be seen from Table 1, progesterone (1·8 mg./kg.) antagonized the action of oestrone (1·7 mg./kg.). Given alone, a single injection of progesterone had no effect on the enzyme in liver or in uterus, even when the dose was increased threefold.

No significant changes in kidney glucuronidase activity were observed in the experiments listed in Table 1.

Table 1. *The glucuronidase activity of mouse liver and uterus after injection of certain steroid hormones*

(In this and all subsequent tables values are given as mean ±S.E. followed (in parentheses) by the number of animals in the group. M. = male, F. = female, O.F. = ovariectomized female.

Glucuronidase activity is expressed in units (G.U.). One G.U. liberates 1 μg. phenol from 0·015M-phenylglucuronide in 1 hr. at 38° at pH 5·2 (for liver, kidney and breast tissue) or at pH 4·5 (for uterus).

In the experiments of Table 1 hormones were administered by single subcutaneous injection of solutions in olive oil.)

Treatment	Sex	Days after treatment	Glucuronidase activity (G.U./g. tissue) Liver	Glucuronidase activity (G.U./g. tissue) Uterus	Uterine weight (mg.)
None	O.F.	—	270±18 (18)	166±21 (18)	36±9 (18)
	M.	—	273±14 (12)	—	—
Oestrone (1·7 mg./kg.)	O.F.	1	431±42 (3)	300±54 (3)	26±5 (3)
	O.F.	4	562±33 (9)	524±56 (9)	210±11 (9)
	M.	1	879±98 (9)	—	—
	M.	4	303±12 (6)	—	—
Oestradiol (2 mg./kg.)	O.F.	1	289±13 (3)	231±12 (3)	62±2 (3)
	O.F.	4	301±15 (3)	357±15 (3)	291±4 (3)
Oestradiol (6 mg./kg.)	O.F.	1	277±16 (3)	257±36 (3)	116±7 (3)
	O.F.	4	287±20 (3)	398±23 (3)	273±10 (3)
	M.	1	292±19 (3)	—	—
	M.	4	279±13 (3)	—	—
Oestriol (2·5 mg./kg.)	O.F.	1	281±17 (3)	209±11 (3)	57±6 (3)
	O.F.	4	306±22 (3)	305±15 (3)	257±11 (3)
Oestriol (5 mg./kg.)	O.F.	1	289±22 (3)	451±38 (3)	275±16 (3)
	O.F.	4	279±26 (3)	500±41 (3)	298±21 (3)
	M.	1	281±17 (3)	—	—
	M.	4	295±18 (3)	—	—
Progesterone (1·8 mg./kg.)	O.F.	1	265±29 (3)	156±8 (3)	38±3 (3)
	O.F.	4	284±15 (3)	167±10 (3)	41±4 (3)
Progesterone (5·4 mg./kg.)	O.F.	1	277±19 (3)	172±12 (3)	33±5 (3)
	O.F.	4	272±19 (3)	189±7 (3)	36±4 (3)
Progesterone (1·8 mg./kg.) + oestrone (1·7 mg./kg.)	O.F.	1	266±24 (3)	188±14 (3)	34±4 (3)
	O.F.	4	289±22 (6)	174±13 (6)	32±3 (6)

Changes in uterus during liver regeneration

In absence of administered oestrogen, small but definite increases in uterine weight and glucuronidase activity occur in ovariectomized mice during liver regeneration (Kerr *et al.* 1949). Further experiments (Table 2) show that administration of testosterone or progesterone (by subcutaneous injection in olive oil) prevented the changes in uterus, without influencing the rise in liver glucuronidase activity, after partial hepatectomy. It should be noted that the rise in uterine weight during liver regeneration was never more than about half that caused by an effective dose of oestrogen (Table 1). Vaginal smears were not unlike those obtained with a dose of oestrone, 0·3 mg./kg. (Kerr *et al.* 1949), which caused a similar increase in uterine weight. Vaginal smears taken from ovariectomized mice during liver regeneration were sent to Prof. G. F. Marrian, F.R.S., who gave us the following opinion: 'The smears were not positive on the basis of the Marrian & Parkes (1929) criteria. In many smears there was a lack of leucocytes and considerable mucification. In some there was a lack of leucocytes and some nucleated epithelial cells were present, while in others cornified cells plus leucocytes were observed. The action appeared to be similar to that observed with a dose of oestrogen just below that required to produce a positive smear on the basis of the Marrian & Parkes (1929) criteria.'

Table 2. *The effects of testosterone and of progesterone on uterus in ovariectomized mice after partial hepatectomy*

(Dose divided between two injections, one 6 hr. after partial hepatectomy, the other 3 days later. Measurements made 8 days after partial hepatectomy. G.U. defined in Table 1.)

Treatment	Glucuronidase activity (G.U./g. tissue) Liver	Glucuronidase activity (G.U./g. tissue) Uterus	Uterine weight (mg.)
None	270±18 (18)	166±21 (18)	36±9 (18)
Partial hepatectomy	559±49 (12)	351±30 (12)	111±13 (12)
Partial hepatectomy + testosterone (4·0 mg./kg.)	572±48 (6)	247±27 (6)	43±7 (6)
Testosterone (4·0 mg./kg.)	283±17 (6)	195±15 (6)	32±4 (6)
Partial hepatectomy + progesterone (3·6 mg./kg.)	509±36 (3)	186±16 (3)	38±5 (3)
Progesterone (3·6 mg./kg.)	282±25 (3)	174±21 (3)	35±2 (3)

The glucuronidase activity of proliferating breast tissue

Fishman & Anlyan (1947) found that the glucuronidase activity of human malignant growths was higher than that of most normal tissues. This observation has been confirmed in mice (Karunairatnam, Kerr & Levvy, 1949). Fishman & Anlyan (1947) also noted that the lactating breast in a human subject had a higher glucuronidase activity than normal breast tissue. Table 3 shows the glucuronidase activity of three spontaneous breast tumours in mice, and of healthy breast tissue at various stages of pregnancy and lactation. Histological examination showed the tumours to be adenocarcinomata. In the absence of any data for the kinetics of hydrolysis of phenylglucuronide by breast or tumour glucuronidase, the enzyme assays were done as recommended for liver and kidney (Kerr *et al.* 1949). In each animal, the mammary glands were pooled before homogenizing and taken through the rest of the procedure in the usual way.

Table 3. *Glucuronidase activities of healthy and malignant breast tissue*

(G.U. defined in Table 1.)

Description	Glucuronidase activity (G.U./g. tissue)
Normal adults (virgin)	92±7 (3)
7–14 days pregnant	173±9 (3)
14–21 days pregnant	165±16 (3)
1 day post-partum	151±19 (4)
11 days post-partum	97±4 (3)
Spontaneous adenocarcinomata (individual results)	197, 423, 454

If the figures in Table 3 may be taken as a guide, proliferation of the breast commenced in the mouse in the early stages of pregnancy and had ceased at 11 days post-partum, although the animals were still lactating at that time. At no stage was the glucuronidase activity of healthy breast tissue as high as in the tumours.

The glucuronidase activity of rat liver

It was considered desirable to examine the relationship between the glucuronidase activity and the state of proliferation of a tissue in another animal than the mouse. Table 4 shows figures obtained for the glucuronidase activity of infant, adult, and regenerating rat liver. Assays were done as described for mouse liver (Kerr *et al.* 1949). Liver glucuronidase activity in 4-day-old rats was more than twice the value for normal adults, and enzyme

activity in liver regenerating after partial hepatectomy was even higher. In individual operated animals, the activity of the portion of liver removed was never more than half the figure for the remaining hypertrophied lobe.

Table 4. *Glucuronidase activity of rat liver*

(G.U. defined in Table 1.)

Description	Glucuronidase activity (G.U./g. tissue)
Normal adults	1382±264 (10)
Normal infants (4-day-old)	2977±301 (4)
Adults, 4 days after partial hepatectomy	3177±541 (6)

Effect of growth inhibitors

Colchicine. In view of the inhibitory action of colchicine on growth processes in general (Lits, Kirschbaum & Strong, 1938), a study was made of its action on the glucuronidase activities of various organs in the mouse. The drug was dissolved in 0·9% sodium chloride solution and injected subcutaneously. As can be seen from Table 5, it had no marked effect on the enzyme levels in normal adults, even in a dose of 6 mg./kg., a dose which is usually rapidly fatal.

Given 6 hr. after partial hepatectomy, colchicine (1·5 mg./kg.) prevented hypertrophy of the remaining fragment of liver and the associated rise in glucuronidase activity (Table 5). When the interval between operation and colchicine injection was increased to 24 hr., regeneration took its normal course. Scheifley & Higgins (1940) found colchicine to be effective in partially hepatectomized rats only if given in the initial stages of recovery. Given within a few minutes of oestrone (1·7 mg./kg.), colchicine (1·5 mg./kg.) antagonized the effects of the oestrogen in liver and uterus in ovariectomized mice.

Table 6 shows results obtained in two experiments with infant mice. In each experiment, a litter was

Table 5. *Action of colchicine in combination with measures leading to changes in glucuronidase activity in adult mice*

(G.U. defined in Table 1.)

Treatment	Sex	Days after initial treatment	Glucuronidase activity (G.U./g. tissue) Liver	Kidney	Uterus	Uterine wt. (mg.)
None	M.	—	273±14 (12)	288±22 (12)	—	—
	F.	—	304±29 (12)	306±25 (12)	318±38 (12)	229±27 (12)
	O.F.	—	270±18 (18)	316±22 (18)	166±21 (18)	36±9 (18)
Colchicine (1·5 mg./kg.)	M.	2	273±22 (3)	277±42 (3)	—	—
	F.	2	243±23 (3)	350±45 (3)	213±14 (3)	194±5 (3)
	F.	4	281±18 (3)	379±19 (3)	205±10 (3)	183±6 (3)
	O.F.	2	282±16 (3)	379±31 (3)	187±22 (3)	39±8 (3)
	O.F.	4	269±22 (3)	357±25 (3)	168±24 (3)	29±3 (3)
Colchicine (3 mg./kg.)	M.	1	233±27 (3)	291±22 (3)	—	—
Colchicine (6 mg./kg.)	M.	1	260±15 (2)	252±18 (2)	—	—
Partial hepatectomy	M.	4	780±50 (6)	360±24 (6)	—	—
Partial hepatectomy + colchicine (1·5 mg./kg.) 6 hr. later	M.	4	243±26 (8)	285±17 (6)	—	—
Partial hepatectomy + colchicine (1·5 mg./kg.) 24 hr. later	M.	4	718±68 (3)	280±38 (3)	—	—
Oestrone (1·7 mg./kg.)	O.F.	1	431±42 (3)	313±17 (3)	300±54 (3)	26±5 (3)
	O.F.	4	562±33 (9)	309±20 (9)	524±56 (9)	210±11 (9)
Oestrone (1·7 mg./kg.) + colchicine (1·5 mg./kg.) simultaneously	O.F.	1	307±9 (3)	370±23 (3)	246±32 (3)	32±2 (3)
	O.F.	4	320±20 (6)	362±19 (6)	251±27 (6)	40±8 (6)

Table 6. *Effect of colchicine in young mice*

(Subcutaneous injection of 1 mg. colchicine/kg. in 0·9% NaCl solution every second day. Litter-mate controls injected with pure NaCl solution. G.U. defined in Table 1.)

Description	Age (days) At start	At end	Average body wt. (g.) At start	At end	Increase in wt. (%)	Glucuronidase activity (G.U./g. liver)
Treated	9	18	6·88	6·70	−2·6	347±31 (4)
Controls	9	18	6·73	11·10	64·9	673±49 (4)
Treated	10	15	7·90	8·00	1·3	310±17 (4)
Controls	10	15	8·10	9·21	13·7	1043±62 (4)

removed from the mother and divided into two groups. One group received repeated injections of colchicine and the other was kept as control. Both groups received the same diet. The control animals had gained in weight and their liver glucuronidase activities were normal for their age (Karunairatnam *et al.* 1949) at the end of each experiment. The colchicine-treated mice, on the other hand, did not gain in weight and their liver enzyme levels fell to within the range for normal adults.

Sorbic acid. 'Parasorbic acid' (D-4-hydroxypent-1-ene-1-carboxylic acid lactone) inhibits the growth of connective tissue (Haynes, 1948). It was considered of interest to investigate the possibility that the related compound, sorbic acid (penta-1:3-diene-1-carboxylic acid), which is readily available, might have a depressant action on tissue growth and glucuronidase activity *in vivo*. It has no effect on the enzyme *in vitro* (Karunairatnam & Levvy, 1949). In the following experiments, sorbic acid (Light & Co. Ltd.) was given to mice by subcutaneous injection of a neutralized solution in 0·9% sodium chloride solution.

Single injections of 160 mg. sorbic acid/kg. had no effect on the glucuronidase activities of liver, kidney and uterus in adult mice (male and ovariectomized female), nor was there any striking change in the histological appearance of the organs. The general picture was unchanged when this dose was repeated on several consecutive days (Table 7).

Table 7. *Effect of sorbic acid on liver, kidney and uterine glucuronidase in normal mice*

(G.U. defined in Table 1.)

Dosage	Sex	Days after injection	Glucuronidase activity (G.U./g. moist tissue) Liver	Kidney	Uterus	Uterine wt. (mg.)
None	M	—	273±14 (12)	288±22 (12)	—	—
	F.	—	304±29 (12)	306±25 (12)	318±28 (12)	229±27 (12)
	O.F.	—	270±18 (18)	316±22 (18)	166±21 (18)	36± 9 (18)
160 mg./kg. injected daily throughout experiment	O.F.	6	258±26 (3)	382±36 (3)	175±20 (3)	41± 8 (3)
	O.F.	10	263±24 (3)	359±25 (3)	168±16 (3)	35± 7 (3)
240 mg./kg. (single injection)	M.	2	284±37 (3)	361±27 (3)	—	—
	M.	4	27±30 (12)	31±25 (12)	—	—
	M.	5	133±21 (3)	234±19 (3)	—	—
	M.	6	240±29 (3)	345±26 (3)	—	—
	M.	9	287±27 (3)	389±24 (3)	—	—
	M.	11	327±18 (3)	394±31 (3)	—	—
	F.	2	275±21 (6)	360±27 (6)	275±19 (6)	247±17 (6)
	F.	4	17± 9 (12)	34±28 (12)	301±20 (12)	202±14 (12)
360 mg./kg. (single injection)	M.	1	259±26 (3)	370±36 (3)	—	—
	F.	2	245±31 (3)	345±28 (3)	265±19 (3)	209±17 (3)

After a single injection of 240 mg. sorbic acid/kg., a profound depression was seen after 4 days in the glucuronidase activities of liver and kidney, but not of uterus (Table 7). Individual animals sometimes showed zero enzyme activities in liver or kidney. With this dose of sorbic acid, necrosis was seen in the liver, but the kidney was apparently normal. A fall in glucuronidase activity in a severely damaged organ has been noted with other poisons (Levvy *et al.* 1948). The histological findings thus provide some explanation for the action of sorbic acid on the enzyme in liver, but not in kidney.

When the dose of sorbic acid was increased to 360 mg./kg., the mice never survived single injections for more than 2 days, by which time any action on the enzyme was not apparent (Table 7). Histological examination revealed severe necrosis in the liver, slight damage in the kidney, and an arrest of mitosis throughout the body. Repeated daily injections of 240 mg./kg. were also rapidly fatal.

Experiments in which infant mice received 160 mg. sorbic acid/kg. (Table 8) yielded results resembling those obtained with colchicine, in that growth was checked and the liver enzyme activity reduced to the adult value.

Many experiments were carried out in which the action of sorbic acid was studied following partial hepatectomy or injection of oestrone or carbon tetrachloride. Results of representative experiments are shown in Table 9. Sorbic acid did not prevent the rise in liver glucuronidase activity which follows injection of carbon tetrachloride (Levvy *et al.* 1948), nor did it influence the changes produced in liver and uterus by oestrone (Table 1). It did, however, prevent the increase in liver enzyme activity and the associated changes in uterus which follow partial hepatectomy (Table 2). The action of sorbic acid in a dose of 240 mg./kg. in depressing kidney glucuronidase activity, observed after 4 days in normal animals (Table 7), was still seen after partial hepatectomy or injection of carbon tetrachloride, but not after oestrone administration. In the livers of partially hepatectomized mice injected with sorbic acid, cell division was frequently seen to be arrested

Table 8. *Effect of sorbic acid in young mice*

(Subcutaneous injection of 160 mg. sorbic acid/kg. as a neutral solution in 0·9% NaCl solution daily. Litter-mate controls injected with pure NaCl solution. G.U. defined in Table 1.)

Description	Age (days)		Average body wt. (g.)		Increase in wt. (%)	Glucuronidase activity (G.U./g. liver)
	At start	At end	At start	At end		
Treated	10	22	8·10	8·95	10·5	290±22 (4)
Controls	10	22	8·10	13·50	66·6	636±29 (4)
Treated	11	22	6·20	6·66	7·4	283±15 (4)
Controls	11	22	6·15	10·15	65·1	574±32 (4)

Table 9. *Action of sorbic acid in combination with measures leading to changes in glucuronidase activity in adult mice*

(G.U. defined in Table 1.)

Other treatment	Sex	Days after other treatment	Glucuronidase activity (G.U./g. tissue)			Uterine wt. (mg.)
			Liver	Kidney	Uterus	
Single injection of 240 mg. sorbic acid/kg. within 1 hr. of other treatment						
CCl_4 (5·3 g./kg.)	M.	4	576±49 (3)	62±28 (3)	—	—
Partial hepatectomy	M	4	298±32 (6)	78±23 (6)	—	—
Oestrone (1·7 mg./kg.)	M.	4	428±32 (3)	367±35 (3)	—	—
Daily injection of 160 mg. sorbic acid/kg. commencing 3 days before other treatment						
CCl_4 (5·3 g./kg.)	M.	7	858±48 (3)	378±25 (3)	—	—
Partial hepatectomy	O.F.	8	325±36 (3)	347±26 (3)	142±18 (3)	46±9 (3)
	M.	8	307±29 (3)	307±32 (3)	—	—
Oestrone (1·7 mg./kg.)	O.F.	4	468±25 (3)	362±29 (3)	377±25 (3)	197±8 (3)

in the metaphase. Displacement of the chromosomes was occasionally observed in cells in late anaphase.

DISCUSSION

In the variety of experiments described above in which a change was observed in glucuronidase activity, the only other common factor would appear to be a change in the state of proliferation of the tissue studied. The results are thus in accordance with the views put forward concerning this enzyme in previous communications (Levvy *et al.* 1948; Kerr *et al.* 1949; Odell & Burt, 1949). In common with the practice of most other workers in this field, our determinations of glucuronidase activity were made with aqueous extracts of freshly homogenized tissue, after a brief period of incubation to coagulate inactive protein. In recent work, carried out at the Rowett Research Institute, we have found that normal mouse liver contains relatively large amounts of an insoluble glucuronidase precursor. Preliminary results suggest that this precursor disappears from liver when the activity of extracts rises after partial hepatectomy. Incubation at acid pH leads to transformation of the precursor into the soluble enzyme, and this occurs to some extent under the conditions used for the final assay of the enzyme. It is evident that varying the mode of preparation of the enzyme for assay may profoundly alter the type of result obtained during changes in the state of proliferation of a tissue. For example, extracts prepared from tissue homogenates which have first been submitted to prolonged incubation may be expected to contain glucuronidase arising from the precursor as well as the enzyme originally present in an active state.

Colchicine had no effect on the glucuronidase activities of normal adult tissues as measured by our own procedure. It did, however, prevent increases in activity following on measures which normally stimulate cell division. It seems probable from these findings that the action of the drug on the activity of the enzyme was secondary to its effect on mitosis, and that the small number of dividing cells in an adult liver or kidney makes a negligible contribution to the total glucuronidase activity.

Sorbic acid arrested growth in infant mice and liver regeneration in partially hepatectomized mice. In these experiments it kept the liver glucuronidase activity at the normal adult level in the same way as colchicine. The failure of sorbic acid to prevent rises in liver and uterine glucuronidase activity in other experiments may have been due to inadequate dosage. The toxicity of the compound, however, precluded increases in dosage. It is possible that the falls in liver and kidney glucuronidase activity produced in normal mice by 240 mg. sorbic acid/kg. may

have been due, not to the compound itself, but to some metabolite, such as parasorbic acid, since the effects were not seen until 4 days after injection. More information is obviously required regarding the action and fate of sorbic acid in the body before its effects on glucuronidase can be fully understood.

It seems probable that the changes seen in uterus during liver regeneration in ovariectomized mice were due to an extra-ovarian oestrogen since they were antagonized by testosterone and by progesterone. The bearing of this finding on certain experiments which claim to show a change in the metabolism of oestrogens during liver damage and regeneration has already been discussed (Kerr *et al.* 1949). Toxicity for liver may explain the actions of some compounds with feebly oestrogenic properties. It seems quite possible that such compounds could cause urinary excretion of a 'true oestrogen', as defined by Emmens (1943).

The action of oestrone on liver was not shared by oestriol and oestradiol under the conditions of our experiments, but it did resemble an oestrogenic action in that it was antagonized by testosterone (Kerr *et al.*·1949) and by progesterone.

SUMMARY

1. Under similar experimental conditions, oestriol and oestradiol do not show the same action as oestrone (Kerr, Campbell & Levvy, 1949) in increasing liver glucuronidase activity in male and ovariectomized female mice. The action of oestrone on liver is antagonized by progesterone.

2. Testosterone and progesterone antagonize the increases in uterine weight and glucuronidase activity seen in ovariectomized mice during liver regeneration (Kerr *et al.* 1949), without affecting the enhanced enzyme activity in liver itself.

3. The glucuronidase activity of mouse breast tissue rose in the early stages of pregnancy and had returned to normal at 11 days post-partum. At no time was the activity in healthy breast tissue as high as in the mammary tumours studied.

4. Colchicine, itself without action on the glucuronidase activities of normal adult mouse tissues, antagonized the effects of measures which cause an increase in activity. Liver glucuronidase activity in infant mice was reduced to the adult value by colchicine.

5. Sorbic acid inhibits cell division to some extent. This does not, however, explain all the effects of the compound on glucuronidase.

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